REMARKS

Prior to the present amendment, claims 1-33 were pending. By this amendment, applicant has amended claims 1 and 2, cancelled claims 3-10 and 13-33, and added new claims 34-36. Accordingly, claims 1, 2, 11, 12, and 34-36 are under examination.

Support for the amendment to claim 1 and new claim 34 can be found in the specification as filed on page 5, lines 20-23. Support for the amendment to claim 2 can be found in original claim 17. Support for new claim 35 can be found on page 5, lines 24-27 of the specification as filed. Support for new claim 36 can be found in the specification as filed on page 5, lines 24-28 and original claims 1 and 5.

Accordingly, no new matter has been entered by the amendments to the claims.

INTERVIEW

Applicant wishes to thank Examiner Leslie A. Royds for taking the time to discuss the office action dated August 21, 2007 with his representatives, Irving N. Feit and the undersigned, by phone interview on October 10, 2007. Applicant's representatives discussed the 35 U.S.C. 112 and 35 U.S.C. 103 rejections with the examiner. In particular, the examiner stated that all remarks and arguments should be submitted in a formal response. Accordingly, applicant submits the following remarks.

CLAIMS

Claim 1 is directed to a method of treating cutaneous facial flushing caused by menopause-associated hot flashes by topically administering at least one selective alpha-2 adrenergic receptor agonist. Applicant has amended claim 1 to specify that the selective alpha-2 adrenergic receptor agonist is at least two-fold to twenty-fold more selective for the alpha-2 adrenergic receptor as compared to clonidine. For example, brimonidine is seven to twelve-fold more selective for the alpha-2 adrenergic receptor as compared to clonidine.

New dependent claim 34 is directed to a selective alpha-2 adrenergic receptor agonist that is at least seven to twelve-fold more selective than clonidine.

New independent claim 36 is directed to a method of treating cutaneous facial flushing caused by menopause associated hot flashes by topical administration of brimonidine tartrate.

OBJECTION

The examiner objected to claim 18 as being a substantial duplicate of claim 12. In the present amendment, applicant has cancelled claim 18. Accordingly, claims 12 and 18 are no longer duplicates.

REJECTION UNDER 35 U.S.C. 112, FIRST PARAGRAPH

The examiner rejected claims 1, 2, 5, 6, 11-13, 18, and 26 under 35 U.S.C. 112, first paragraph for not being enabling for the prevention of cutaneous flushing caused by menopause-associated hot flashes. Applicant has amended independent claim 1 to delete the word "prevent." Independent claim 26 has been cancelled. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

REJECTIONS UNDER 35 U.S.C. 112, SECOND PARAGRAPH

Claims 1, 2, 5, 6, 11-13, 18, and 26 were rejected under 35 U.S.C. 112, second paragraph, for being indefinite. The examiner stated that applicant did not make clear on the record whether a human is in need of treatment of cutaneous flushing. The examiner also stated that the applicant had failed to clearly connect the therapeutic objective of the preamble, *i.e.*, treating cutaneous flushing, with the effective amount to be administered.

Applicant has amended claim 1 to specify that the method is directed to reducing cutaneous flushing in a human in need thereof. Additionally, applicant has cancelled

independent claim 26. Reconsideration and withdrawal of the rejection is respectfully requested.

REJECTION UNDER 35 U.S.C. 103

Claims 1, 2, 5, 6, 11-13, 18, and 26 were rejected under 35 USC 103(a) as being unpatentable over Wymenga, et al., "Management of Hot Flushes in Breast Cancer Patients," Acta Oncologia, 41(3), 2002, pgs. 269-275 ("*Wymenga*") in view U.S. Patent Publication No. 2003/0229088 to Gil, et al. ("*Gil*").

A. Wymenga *does not disclose topical administration*

According to the examiner, *Wymenga* discloses that clonidine, a centrally active alpha-adrenergic agonist, when administered orally or transdermally in low dosages is demonstrated to be effective in the reduction of hot flushes caused by normal menopause. Applicant respectfully disagrees with the examiner's analysis.

As noted by the examiner, *Wymenga* discloses only oral or transdermal administration of clonidine, both of which are forms of **systemic** administration. See the sentence bridging pages 12 and 13 of the office action.

By contrast, the presently claimed invention is limited to **topical** administration of alpha-2 adrenergic receptor agonists to treat facial flushing associated with menopause-associated hot flashes. *Wymenga* discloses nothing about topical administration.

It is well known that topical administration is very different from systemic administration. For example, drugs administered systemically enter the bloodstream, and therefore are delivered throughout the body. Drugs administered topically, on the other hand, do not enter the bloodstream in significant amounts.

A composition according to the invention is currently in clinical trials. The composition contains brimonidine tartrate in a facial gel. During Phase I testing, the

composition was administered topically to the faces of sixteen subjects. Following administration, each individual's plasma concentration of brimonidine was measured. For each individual, the plasma concentration of brimonidine was below the limit of quantification. Accordingly, brimonidine administered topically does not enter the bloodstream in significant amounts. See the Draft Clinical Study Report on page 4 under the heading "Statistical Methods" which is being submitted with the Supplemental Information Disclosure Statement filed herewith.

In view of the significant differences between topical and systemic administration of drugs, one of ordinary skill would not be able to predict the effectiveness of topical administration, as presently claimed, based upon the effectiveness of oral or transdermal administration, as disclosed in *Wymenga*. For example, a person suffering from a headache might take an aspirin to relieve the symptoms of the headache. However, the person would not predict that rubbing aspirin on his or her forehead would relieve the headache.

Accordingly, *Wymenga's* conclusions regarding orally or transdermally administered clonidine do not render topical administration of different compounds obvious.

B. Wymenga's *conclusions are limited to administration of clonidine and cannot be extrapolated to selective alpha-2 adrenergic receptor agonists, much less to brimonidine.*

Wymenga only discusses the effectiveness of the alpha agonist, clonidine. Clonidine, however, is not a selective alpha-2 adrenergic receptor agonist according to the invention. A "selective alpha-2 adrenergic receptor agonist" is defined in the specification on page 5, lines 20-23 as being at least two-fold to twenty-fold more selective for the alpha-2 adrenergic receptor as compared to clonidine.

In amended claim 1, the "selective alpha-2 adrenergic receptor agonist" is required to be at least two-fold to twenty-fold more selective for the alpha-2 adrenergic receptor as compared to clonidine. See amended claim 1 and page 5, lines 20-23 of the application as filed.

The conclusions in *Wymenga* regarding clonidine are limited to systemic administration of clonidine. *Wymenga's* conclusions with respect to systemic administration of clonidine to reduce menopausal flushing cannot be extrapolated even to topical administration of clonidine for this purpose, much less to topical administration of a selective alpha-2 adrenergic receptor agonist. Therefore, *Wymenga* does not render the claimed selective alpha-2 adrenergic receptor agonists obvious.

C. Gil *does not disclose brimonidine and clonidine as being functionally equivalent.*

The examiner acknowledges that *Wymenga* fails to specifically teach the use of the alpha-2 adrenergic agonist, brimonidine tartrate.[1] The examiner attempts to make up for this deficiency by citing *Gil*. The examiner contends that one of ordinary skill in the art would have used the brimonidine alpha-adrenergic agonist as taught by *Gil* for the treatment of menopausal hot flushes because *Gil* discloses that brimonidine and clonidine are functionally equivalent for binding the alpha-adrenergic receptors.

Gil is not relevant to the present invention for at least the reasons given below.

According to the examiner: "[T]he brimonidine (or tartrate salt thereof) of Gil et al. was functionally equivalent for binding the alpha-adrenergic receptor as the clonidine compound disclosed by Wymenga, et al."[2] Applicant respectfully disagrees with the examiner's statement.

It is true that *Gil* discloses that both clonidine and brimonidine are alpha-adrenergic receptor agonists.[3] But *Gil* does not disclose that they are functionally equivalent.

Evidence that brimonidine and clonidine are, in fact, not equivalent alpha adrenergic receptors may be found in an article of Burke et al., *Survey of Ophthalmology* 41, Supp. 1,

[1] See the first full paragraph on page 13 of the office action.
[2] See the last paragraph on page 13 of the office action.
[3] See paragraph 49.

S9-S18 (1996) (*Burke*). *Burke* was previously submitted in the Information Disclosure Statement filed on April 16, 2004.

Burke reports that brimonidine is seven to twelve times more alpha-2 selective relative to alpha-1 than is clonidine.[4] As a result, topical brimonidine was reported to be less vasoconstrictive in a model designed to assess the vasoactivity of the human retinal microvasculature.[5] Accordingly, *Burke* provides strong evidence that brimonidine and clonidine are not equivalent alpha adrenergic receptors.

It is important to note that the claimed invention is directed to selective alpha-2 adrenergic receptor agonists that are at least two-fold to twenty-fold more selective for the alpha-2 adrenergic receptor as compared to clonidine. As discussed above, brimonidine is seven to twelve-fold more selective for the alpha-2 adrenergic receptor as compared to clonidine. Therefore, brimonidine and clonidine are clearly not functionally equivalent alpha adrenergic receptors with respect to the present invention. Consequently, one of ordinary skill in the art would not be able to predict that brimonidine can be substituted for clonidine.

D. Gil *only relates exclusively to a method of alleviating pain.*

Gil discloses nothing more than a method of alleviating pain by administering an alpha-adrenergic agonist, such as brimonidine or clonidine. The examiner contends that *Gil* "confirms the amenability of brimonidine into a dermatologically acceptable formulation."[6] Nevertheless, there is no disclosure in *Gil* that brimonidine is suitable to treat any dermatological condition.

The examiner's argument is not relevant to claim 1. As mentioned above, clonidine does not fall under claim 1 because it is not a selective alpha-2 adrenergic receptor agonist according to the invention.

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[4] See, the abstract, lines 1 and 2, and page S10, column 1, second full paragraph at lines 1-5.
[5] See the abstract at lines 8 and 9 and the sentence bridging columns 1 and 2 on page S14.
[6] See lines 5-6 of page 14 of the office action.

With respect to independent claim 36, applicant disagrees with the examiner's arguments. Even if *Gil* taught that clonidine and brimonidine are functionally equivalent for treating pain, which it does not for at least the reasons set forth in section C, *Gil* still would not teach that clonidine and brimonidine are functionally equivalent for treating facial flushing associated with menopause-associated hot flashes. Treating pain, as is disclosed in *Gil*, cannot be said to be the equivalent of treating facial flushing associated with menopause-associate hot flashes, as is currently claimed. Pain is clearly very different from facial flushing associated with menopause-associated hot flashes.

For example, pain is mediated by adrenergic receptors on **sensory nerve cells**. By contrast, facial flushing associated with menopause-associated hot flashes is mediated by adrenergic receptors on **smooth muscle cells**. One cannot predict the effect of adrenergic receptors on smooth muscle cells from the effect of adrenergic receptors on sensory nerve cells. Therefore, one cannot extrapolate the result of treating pain to treating menopause-associated flushing.

Conclusion

For at least the above reasons, a person having ordinary skill in the art would not understand that oral or transdermal clonidine, as taught in the prior art, is the functional equivalent of a topical selective alpha-2 adrenergic receptor agonist, as currently claimed.

First, the skilled person would understand that the efficacy of **oral or transdermal** clonidine for treating flushing associated with menopause, does not predict that **topical** administration of a selective alpha-2 receptor agonist is effective to treat the same condition. Moreover, the skilled person would have no reason to substitute clonidine for a selective alpha-2 adrenergic receptor agonist. Clonidine is not a selective alpha-2 adrenergic receptor agonist as defined in the specification. Furthermore, clonidine is not functionally equivalent to brimonidine, which is seven to twelve-fold more selective for the alpha-2 adrenergic receptor as compared to clonidine. Finally, a person skilled in the art would not even understand that oral clonidine is the functional equivalent of topical brimonidine for treating

a particular type of pain, which was the particular concern of *Gil*, let alone for reducing a condition as different from pain as facial flushing associated with menopause-associated hot flashes, which was never mentioned in *Gil*.

Applicant respectfully submits that the application is now in proper form for allowance, which action is earnestly solicited. If resolution of any remaining issue is required prior to allowance of the application, it is respectfully requested that the examiner contact applicant's attorney at the telephone number provided below.

If any additional fees are due or any overpayment has been made in connection with this paper, please charge or credit Deposit Account No. 08-2461 for such sum.

Respectfully submitted,

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